Magnesium and the Cardiometabolic Syndrome

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Published online: 14 March 2012
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Abstract The cardiometabolic syndrome is a cluster of metabolic factors that increase an individual's risk of developing cardiovascular disease and type 2 diabetes mellitus. The metabolic risk factors that cluster in the syndrome include insulin resistance, hypertension, impaired glucose tolerance, central obesity, and dyslipidemia. Other abnormalities, such as chronic proinflammatory and prothrombotic states and oxidative stress, have been added to the syndrome. Magnesium (Mg) plays a key role in regulating insulin action, glucose uptake, and vascular tone. Many experimental, clinical, and epidemiologic studies have shown a clear link between Mg status and any component included in the constellation. Increasing evidence suggests a role for Mg deficiency as a possible unifying mechanism underlying the coincidence among those apparently disparate clinical conditions clustering in the syndrome. Although the use of Mg supplements has been suggested as a potential tool in the prevention of the cardiometabolic syndrome, this needs to be demonstrated by future prospective studies.

Keywords Magnesium · Calcium · Cardiometabolic syndrome · Metabolic diseases · Cardiovascular disease · Type 2 diabetes mellitus · Insulin resistance · Glucose intolerance · Blood pressure · Hypertension · Dyslipidemia · Visceral adiposity · Coagulation factors · Inflammation · Oxidative stress · Aging

Introduction

Magnesium (Mg) is the second most abundant intracellular cation after potassium present in living cells. Most of the Mg present in the adult human body is distributed in the intracellular compartment (99%), with only 1% in the extracellular fluid [1]. The small intestine is the main site of Mg absorption, whereas Mg excretion is mainly performed through renal pathways. Serum Mg exists in three forms: a protein-bound fraction (25% bound to albumin and 8% bound to globulins), a chelated fraction (12%), and the metabolically active ionized fraction (Mg^{2+} ion, 55%) [2]. Even if there is no known hormonal factor specifically involved in the regulation of Mg metabolism, several hormones are recognized to have an effect on Mg balance and transport, such as parathyroid hormone, calcitonin, and catecholamines. A major role for insulin has been proposed, and accumulating data have confirmed that insulin is a key hormone in the regulation of Mg metabolism [1, 3]. Insulin has specific ionic effects to stimulate the transport of Mg from the extracellular to the intracellular compartment, thus increasing Mg intracellular content [4].

Cardiometabolic Syndrome

The cardiometabolic syndrome (CMetS) is the name for a clustering of interconnected metabolic factors that increase the risk for the development of cardiovascular disease, other forms of atherosclerotic diseases, and type 2 diabetes mellitus (T2DM) [5, 6]. The prevalence of CMetS varies and depends on the criteria used in different definitions, as well as the composition (sex, age, race, and ethnicity) of the population studied [7]. Metabolic risk factors that cluster in the syndrome include insulin resistance (IR), elevated

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blood pressure (BP), impaired glucose tolerance, central obesity, and dyslipidemia. Other abnormalities, such as chronic proinflammatory and prothrombotic states, as well as oxidative stress, have been added to the syndrome, making its definition even more complex.

Besides the many components and clinical implications of CMetS, there are hitherto no universally accepted pathogenetic mechanisms or diagnostic criteria [7]. Following the initial definition of syndrome X by Reaven [8], many international organizations and expert groups, such as the World Health Organization (WHO), the European Group for the Study of IR, the National Cholesterol Education Program Adult Treatment Panel III (NCEP:ATPIII), the American Association of Clinical Endocrinologists, the International Diabetes Federation (IDF), and the American Heart Association/National Heart, Lung, and Blood Institute, have used different parameters to define CMetS; each definition focuses mainly on a specific aspect of the cluster (eg, glucose for WHO definition, central obesity for the IDF one, dyslipidemia and other common cardiovascular risk factors for the NCEP:ATPIII definition) [6•]. Furthermore, the debate as to whether CMetS represents a specific syndromic entity, or whether it should be considered only a frequent association of independent cardiovascular risk factors is still unresolved. Therefore, some authors have suggested that the components of the syndrome should be evaluated and treated without regard to whether a patient meets the criteria for diagnosis of the CMetS [9]. However, independent of the diagnostic criteria used, CMetS has a high and increasing prevalence in all Western societies, mostly due to the growing obesity epidemic [6•, 7]. In the United States, according to the National Health and Examination Survey (NHANES) 2003 to 2006, approximately 34% of people studied met the NCEP:ATPIII criteria for CMetS, with a significant increase compared with previous surveys [10]. The more restrictive WHO criteria showed nearly the same prevalence of CMetS, whereas the IDF definition, which adopted a lower cutoff point for waist circumference, estimated an even higher prevalence [11]. Individuals with CMetS, independently of the diagnostic criteria used, have an increased risk for the development of cardiovascular diseases and associated mortality, as confirmed by epidemiologic and prospective studies [12–15] and by a recent meta-analysis [16•]. Although CMetS includes a constellation of cardiovascular, renal, metabolic, prothrombotic, and inflammatory abnormalities, the two major interacting features that are the core and the hallmark of the syndrome are IR/hyperinsulinemia/reduced peripheral glucose utilization and visceral obesity.

Although it is apparent that an interaction between genetic and environmental factors may contribute to the pathophysiology of CMetS, many aspects underlying the abnormalities and physiologic disturbances of the syndrome remain unclear. Mg has been suggested to play a key role in

the pathogenesis of CMetS, as confirmed by many experimental, clinical, and epidemiologic studies that have shown a clear link between Mg status and any individual component included in the constellation [1].

Magnesium and the Cardiometabolic Syndrome Components

Magnesium and Hypertension

Mg ion, although not directly involved in the biochemical process of contraction, modulates vascular smooth muscle tone by affecting calcium ion concentrations. In particular, Mg regulates the activity of many plasma membrane and cellular ion transport pump mechanisms that maintain the critical cytosolic concentrations of calcium and sodium, hence affecting baseline tension, vascular tone, and responsiveness to pressor agents [17]. Experimental dietary Mg deficiency has been associated with vasoconstriction, frank hypertension, potentiated atherosclerosis, increased thromboxane synthesis, and IR, all conditions frequently associated with the CMetS [18, 19]. Epidemiologic studies have suggested an inverse relationship between Mg intake and BP, with lower dietary Mg intake being an independent predictor of hypertension [20]. In experimental and in human hypertension, decreased Mg levels have been reported in several tissues (eg, heart, lungs, kidney, bone, skeletal muscle, blood vessels, and brain) and cell types (eg, vascular smooth muscle cells, fibroblasts, erythrocytes, platelets, and lymphocytes), all confirming the profound alterations of Mg metabolism in hypertensive disease [1, 21–23]. Individuals with essential hypertension have consistently lower concentrations of intracellular free Mg (Mgi) than normotensive controls, and a strong, continuous inverse relationship is present between Mgi and the height of BP; that is, the lower the Mgi, the higher the BP, confirming the existence of a link between Mg depletion and human essential hypertension [21–23]. Metabolic conditions, including hypertension, CMetS, and T2DM, share a common altered intracellular environment characterized at least in part by suppressed Mgi levels and reciprocally elevated cytosolic calcium [23]. Mgi levels are related not only to the height of BP but also to the presence of peripheral IR [24], and alterations of Mg metabolism have been suggested as one of the pathogenic mechanisms contributing to the development of IR and CMetS [1, 24–26]. Moreover, the common alterations of intracellular ionic species in different IR conditions support the concept of an ionic basis underlying the frequent coincidence of the different clinical conditions associated with the CMetS. Altered levels of Mgi also have been found to be associated with structural indices of the cardiovascular system. Suppressed Mgi levels are associated

with increased echocardiographically measured posterior wall thickness and left ventricular mass index in hypertensive individuals [27]. Similarly, aortic distensibility determined by MRI in healthy and hypertensive humans was closely and positively related to levels of Mgi measured in situ in brain and skeletal muscle tissue by ^{31}P -nuclear magnetic resonance (NMR) spectroscopic techniques—the more suppressed the Mgi, the stiffer (less distensible) the aorta [28]. Mg deficiency is also associated with impaired endothelial-mediated vasorelaxation, and oral Mg supplementation has been shown to improve endothelial function in patients with coronary artery disease [29] and in hypertensive diabetic individuals [30•].

Mg metabolism is also linked to the renin-angiotensin-aldosterone system (RAAS). In high renin hypertensive individuals, serum ionized Mg tends to be lower and Mg supplementation decreases AngII-stimulated production and aldosterone release [31, 32]. These actions of Mg may help explain the relationship with other CMetS components, also connected to the RAAS (IR, increased oxidative stress, reduced nitric oxide bioavailability, and increased synthesis of proinflammatory cytokines [see below]). Mg also modulates sympathetic nervous system activity. An increase in BP together with an increase in catecholamine excretion and renal sympathetic activity have been shown in Mg-deficient rats [33].

Mg was first recommended to lower BP in patients with malignant hypertension more than 85 years ago, as early as 1925 [34]. However, a consistent, reproducible effect of oral Mg supplementation on BP (except in preeclampsia) is still to be confirmed in essential hypertension [26]. Mg supplementation has been shown to decrease BP in many, but not all clinical studies [35–37], and a focused, large clinical trial is still lacking.

Magnesium, Glucose Intolerance, Insulin Resistance, and Diabetes

Mg ion plays a key role in regulating insulin actions and insulin-mediated glucose uptake. Mg is a necessary cofactor in more than 300 enzymatic reactions, including all the rate-limiting enzymes of glycolysis, and specifically in all phosphorylation processes and in all reactions that involve adenosine triphosphate (ATP) utilization and transfer. Mg deficiency may result in disorders of insulin receptor tyrosine kinase activity as well as all other protein kinases in the insulin signaling, events related to the development of post-receptor IR and decreased cellular glucose utilization [1]. Measurements of intracellular free Mg concentrations using ^{31}P -NMR have revealed that Mgi concentrations are in the 100 to 300 nM range, which is close to the dissociation constant of many enzymatic systems using ATP or phosphate transfer; this confirms the clinical significance of Mg deficiency because of its crucial role as cofactor in many

enzymatic reactions regulating glucose metabolism. In turn, because tissue Mg uptake is regulated by insulin, impairment of this process by CMetS-associated IR may cause or exacerbate intracellular Mg deficiency. The hypothesis that alterations in Mg metabolism may induce and/or exacerbate IR is confirmed by data in both humans and experimental animals, showing that dietary-induced Mg deficit is correlated with IR, lower fasting insulin concentrations, and insulin responses to an oral glucose load [1]. Intracellular Mg levels have been found to quantitatively and inversely predict the fasting and postglucose levels of hyperinsulinemia, peripheral insulin sensitivity, and systolic and diastolic BP [1, 3, 21–24, 26]. Specifically, fasting insulin levels, the integrated insulinemic response to a standard oral glucose tolerance test, and the steady-state plasma glucose response to insulin infusion and indices of peripheral insulin sensitivity derived from euglycemic hyperinsulinemic clamps all have been found to be inversely related to Mg levels, whether measured as Mgi in situ in the brain, free or total Mg in peripheral red cells, or even as circulating Mg. Furthermore, inverse relations have been observed between steady-state fasting levels of Mgi and 1) fasting blood glucose; 2) BP; 3) glycated hemoglobin (HbA_{1c}); and 4) the glycemic and insulinemic response to oral glucose loading in healthy, hypertensive, and diabetic individuals—the lower the Mgi, the higher the BP and the hyperinsulinemic response to oral glucose loading [1, 3, 21–24, 26].

There is evidence consistently showing a deficiency in intracellular, in serum total, and/or in serum ionized Mg in patients with T2DM and/or the CMetS [1, 23, 38, 39]. A deficient Mg status may be a secondary consequence or may precede and cause IR and altered glucose tolerance. Among the mechanisms that may favor Mg depletion in the CMetS, the most important are low Mg intake and increased Mg urinary loss, while dietary Mg absorption and retention seem to remain unaffected. With regard to low Mg intake, changes in dietary habits in the direction of a Westernized pattern have resulted in a frequent occurrence of Mg intake below the recommended daily allowances. Hyperinsulinemia associated with CMetS may contribute to urinary Mg depletion, while the reduced insulin sensitivity itself may affect Mg transport. All together, independent of the cause of poor plasma and intracellular Mg content, Mg depletion is a contributor to further derangement of IR [1]. Reduced serum Mg levels are associated with an increased risk of developing glucose intolerance, CMetS, and T2DM [40]. The frequent inadequacy of Mg metabolism with aging has been suggested to play a role in the increased incidence of age-associated vascular and metabolic conditions such as hypertension, atherosclerosis, T2DM, and CMetS [41••, 42••, 43–45]. All together, regardless of the cause of poor plasma and intracellular Mg content, a depletion of Mg seems to contribute to an impairment of insulin sensitivity.

Mg deficiency, which may take the form of a chronic, latent Mg deficit rather than a clinically evident hypomagnesemia, is crucial because of the previously described key role of Mg as a cofactor in many enzymatic reactions regulating glucose metabolism. Thus, deficient Mg status may not just be a secondary consequence of diabetes but may precede and contribute itself to the development of IR and altered glucose tolerance. Mg depletion promotes tissutal IR and altered vascular tone, suggesting a possible mechanism underlying the coincidence among apparently disparate clinical conditions of IR. We have suggested a role for Mg deficit as a unifying mechanism of conditions associated with IR, including hypertension, T2DM, and CMetS (Fig. 1) [1, 26, 45]. The hypothesis that alterations in Mg metabolism induce IR is confirmed by data in experimental animals and humans showing that dietary-induced Mg deficiency is correlated with IR. A Mg-deficient diet in sheep was associated with a significant impairment in insulin-mediated glucose uptake [46]. Higher Mg intake is associated with lower fasting insulin concentrations among women without diabetes [47], and a significant negative correlation is present between total dietary Mg intake and the insulin responses to an oral glucose tolerance test [48]. Rats fed a low-Mg diet showed a significant increase in blood glucose and triglyceride levels [49]. The effects of dietary-induced Mg deficiency on glucose disposal, glucose-stimulated insulin secretion, and insulin action on skeletal muscle were studied in rats fed a low-Mg-containing diet. Mg depletion provoked a deleterious effect on glucose metabolism due to an impairment of both insulin secretion and action [50]. The IR observed in the skeletal muscles of Mg-deficient rats was linked, at least in part, to a defective tyrosine kinase activity of insulin receptors [51].

Magnesium and Other Components of the Cardiometabolic Syndrome Constellation (Dyslipidemia, Visceral Adiposity, Coagulation Factors)

The relationship between Mg status and lipid profile is less clear than that between BP and IR described above, with studies presenting conflicting results depending on the population examined [52, 53]. Mg is a modulator of HMG-CoA reductase, which catalyzes the rate-limiting step in cholesterol synthesis. In vitro studies have shown that increasing Mg concentration in the bathing solution attenuates HMG-CoA reductase activity [54], and rats fed a Mg-deficient diet show increased serum triglycerides and reduced high-density lipoprotein cholesterol, together with reduced serum activity of lipoprotein lipase [55]. Several other studies have examined the effect of Mg supplementation on lipid levels and have shown a reduction in serum triglyceride levels [56–58] or no effect on the lipids examined [59]. Visceral adiposity is another major component of the CMetS associated with a state of IR and impaired glucose tolerance [5, 6•, 7, 52]. Mg deficiency status was found in Zucker obese rats [60] and in clinical obesity in individuals with IR [61]. In patients with T2DM, Corica et al. [38] found a strong correlation between serum ionized Mg and several components of the CMetS (plasma triglycerides, waist circumference, and microalbuminuria). Mg deficiency may also contribute to the development of IR in obese children [62, 63]. Mazur et al. [60] reported that feeding obese animals a high-Mg diet reduced body weight, improved insulin sensitivity, normalized serum lipids, and corrected plasma Mg content.

An increased platelet reactivity and a prothrombotic state (increased levels of plasminogen activator inhibitor-1 [PAI-1],

Fig. 1 Overall hypothesis in which chronic magnesium (Mg) deficit has been proposed as a link to help explain the clinical coincidence of hypertension, type 2 diabetes mellitus, insulin resistance, dyslipidemia, and atherosclerosis in the cardiometabolic syndrome. CNS, central

nervous system; CRP, C-reactive protein; IL, interleukin; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; TNF, tumor necrosis factor

fibrinogen, and other coagulation factors) are commonly associated with CMetS. Nadler et al. [19, 64] suggested that intracellular Mg deficiency may cause increased platelet reactivity and thromboxane synthesis. Mg therapy may have antithrombotic effects and has been shown to decrease platelet aggregation [65, 66].

Magnesium, Inflammation, and Oxidative Stress

An increased inflammatory state is frequently associated with glucose disorders and metabolic diseases [67, 68]. Inflammation and oxidative stress have been proposed as the possible link between Mg deficit and IR/CMetS [69–72]. More generally, chronic hypomagnesaemia and conditions commonly connected with Mg deficiency, such as T2DM and aging, are associated with increased free radical formation and subsequent damage to cellular processes. Poor Mg status may trigger the development of a low-grade chronic inflammatory state and an increased production of free oxygen radicals. Several experimental and clinical studies have shown that Mg deprivation causes marked elevation of proinflammatory molecules, causing excessive production and release of tumor necrosis factor (TNF)- α , interleukin (IL)-1, IL-6, vascular cell adhesion molecule-1, and PAI-1; increased circulating inflammatory cells; and increased hepatic production and release of acute-phase proteins (ie, complement, α 2-macroglobulin, fibrinogen) [73–77]. Experimental studies in rats have shown that Mg deficiency induces a chronic impairment of redox status associated with inflammation, which could contribute to increased oxidized lipids and may promote IR, β -cell dysfunction, hypertension, and vascular disorders [1, 69–72, 78]. In humans, clinical data have shown that low serum Mg levels as well as inadequate dietary Mg are strongly related to low-grade systemic inflammation. Using the 1999 to 2000 NHANES database, King et al. [69] found that dietary Mg intake was inversely related to serum C-reactive protein (CRP) levels. Among the 70% of the population not taking supplements, Mg intake below the recommended daily allowance was significantly associated with a higher risk of having elevated CRP [69]. Data from the Women's Health Study have shown that Mg intake is inversely related to systemic inflammation measured by CRP concentrations and with the prevalence of the CMetS in adult women [72]. Other studies have confirmed an inverse relationship among Mg intake, serum Mg, and TNF- α , IL-6, and CRP levels [70, 71]. In a cross-sectional study, a higher TNF- α concentration was inversely correlated with serum Mg, and in a multivariate analysis, those individuals with the lowest serum Mg were 80% more likely to have higher circulating levels of TNF- α [71]. In men from the Health Professionals' Follow-Up study, higher Mg intake was associated with higher adiponectin levels

[79]. In experimental animal models and in humans, Mg deficiency has been associated with increased oxidative stress and decreased antioxidant defense, due at least in part to increased inflammation parameters [78, 80–82]. More generally, chronic hypomagnesaemia and conditions commonly associated with Mg deficiency, such as T2DM and aging, are associated with an increase in free radical formation, with subsequent damage to cellular processes [1, 80, 81]. Previous studies have shown convincingly that Mg deficiency results in increased production of oxygen-derived free radicals in various tissues, increased free radical-elicited oxidative tissue damage, increased production of superoxide anion by inflammatory cells, decreased antioxidant enzyme expression and activity, decreased cellular and tissue antioxidant levels, and increased oxygen peroxide [78, 82]. In experimental diabetes, a decreased intracellular Mg level and increased Mg urinary excretion were associated with increased plasma malondialdehyde and a decreased expression of hepatic superoxide dismutase (SOD) and glutathione S-transferase, with all these effects being corrected by Mg supplementation [83]. Mg deficiency in rats also causes decreased hepatic glutathione, SOD, and vitamin E together with increased lipid peroxidation and malondialdehyde levels secondary to upregulated NADPH oxidase activity [84]. Furthermore, Mg itself may possess antioxidant properties, scavenging oxygen radicals, possibly by affecting the rate of spontaneous dismutation of the superoxide ion [82]. Intervention studies in animal models of Mg deficiency have also provided convincing evidence of the link among Mg, inflammation, and oxidative stress. In stroke-prone spontaneously hypertensive rats, Mg deficiency results in marked increases in systolic BP, blunted endothelial function, superoxide accumulation, and mitogen-activated protein kinase activation, all of which were attenuated with a SOD mimetic [85]. Intervention studies have shown that treatment with antioxidant therapies (eg, vitamin C, vitamin E, and glutathione) improves insulin sensitivity in diabetic individuals. Improvement in endogenous antioxidant capacity (GSH:GSSG ratio) and blunting of oxidative stress (decreased GSH:GSSG, increased lipohydroperoxides, increased TBARS, and decreased total antioxidant capacity) were associated with improved cellular Mg homeostasis and improved whole body glucose disposal [86, 87]. All together, data are consistent with a role of Mg deficiency in reducing antioxidant capacity and in promoting oxidative stress, inflammation, and lipid oxidation, and thus with a role of oxidative stress and inflammation in the Mg deficiency-related development of IR, CMetS, and T2DM [1, 26, 45].

Dietary Magnesium and the Cardiometabolic Syndrome

Data from several epidemiologic studies have confirmed a clear link among dietary Mg status, T2DM, and CMetS,

suggesting that increased Mg consumption is associated with a reduced development of T2DM [88] and CMetS [72, 89]. In a prospective study of almost 85,000 women from the Nurses' Health Study and the Health Professionals' Follow-Up Study, the relative risk of developing T2DM for women in the highest quintile of Mg consumption was 0.68 when compared with women in the lowest quintile [88]. In more than 11,000 middle-aged women from the Women's Health Study, Song et al. [72] reported an inverse association between dietary Mg intake and CMetS prevalence. In a longitudinal analysis of 4,637 young adults within the CARDIA (Coronary Artery Risk Development in Young Adult Men) study, He et al. [89] found that Mg intake was inversely related to incident CMetS, each of its components, and fasting insulin levels. In the Women's Health Study, a cohort of 39,345 US women older than 45 years of age were observed for an average of 6 years; a significant inverse association was found between Mg intake and the risk of developing T2DM, further supporting a protective role of high Mg intake in reducing the risk of becoming diabetic [90]. High Mg intake also lowered the concentrations of markers of systemic inflammation and endothelial dysfunction [91].

Thus, data suggest that the use of Mg supplements may be a potential tool for the prevention of T2DM and the CMetS [92]. The effects of Mg supplements on the metabolic profile of diabetic individuals are controversial, with benefits having been found in some [93], but not all clinical studies [94]. Differences in baseline Mg status, age, and variability of diabetic clinical control, duration, and complications may explain the differences among studies. A meta-analysis of nine randomized, double-blind, controlled studies, indicated that oral Mg supplementation for 3 months was effective in lowering fasting serum glucose levels in T2DM patients [95], in accordance with the physiologic role of Mg, to modulate cellular glucose utilization and insulin signaling [1]. The high content of Mg in whole grains has suggested that Mg may mediate their favorable impact on insulin sensitivity [96]. Oral Mg supplementation has been suggested to be beneficial with regard to fasting and postprandial glucose levels and insulin sensitivity in type 2 diabetics with a severe Mg deficit [3, 93]. Among nondiabetic, apparently healthy individuals, there is also some evidence of a relatively small but significant beneficial effect of Mg supplementation on insulin sensitivity [97].

Conclusions

Mg is emerging as a key player in CMetS pathogenesis, as evidenced by the numerous experimental, clinical, and epidemiologic studies delineating a clear link between Mg status and each of the CMetS components (Fig. 1).

Notwithstanding the antihypertensive, anti-inflammatory, antioxidant properties of Mg, it is crucial to remember the strong and unquestionable pathophysiologic link between Mg and insulin sensitivity and action. That no large clinical trial with Mg supplementation has been specifically focused on individuals with Mg deficit may help explain the discrepancy between the epidemiologic evidence of a clear role of Mg deficit in the pathophysiology of the CMetS and the still uncertain benefit of oral supplemental Mg on IR. Long-term prospective studies evaluating the effects of Mg supplements on the development of CMetS and/or T2DM in populations with Mg deficiency are still needed to narrow this gap.

Disclosure No potential conflicts of interest relevant to this article were reported.

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